

1. A non-naturally occurring nucleic acid comprising a nucleotide sequence that (a) encodes a functional ND4 mitochondrial protein and (b) that differs from a naturally occurring nucleic acid that encodes a ND4 mitochondrial protein by at least one
5 codon substitution.

2. The non-naturally occurring nucleic acid of claim 1, wherein the codon substitution is replacement of a mitochondrial codon with a nuclear codon.

10 3. The non-naturally occurring nucleic acid of claim 1, wherein the codon substitution is UGA to UGG.

4. The non-naturally occurring nucleic acid of claim 1, wherein the codon substitution is AGA or AGG to UAA, UAG, or UGA.

15 5. The non-naturally occurring nucleic acid of claim 1, wherein the codon substitution is AUA or AUU to AUG, CUG, or GUG.

20 6. The non-naturally occurring nucleic acid of claim 1, wherein all UGA codons are substituted with UGG codons; all AGA and AGG codons are substituted with UAA, UAG, or UGA codons; and all AUA and AUU codons are substituted with AUG, CUG, or GUG codons.

25 7. The non-naturally occurring nucleic acid of claim 1, wherein the nucleotide sequence comprises the sequence of SEQ ID NO:1.

8. The non-naturally occurring nucleic acid of claim 1, wherein the non-naturally occurring nucleic acid is comprised within an expression vector.

30 9. The nucleic acid of claim 8, wherein the expression vector is a plasmid.

10. The non-naturally occurring nucleic acid of claim 1, wherein the non-naturally occurring nucleic acid is comprised within an rAAV virion.

5 11. The non-naturally occurring nucleic acid of claim 1, wherein the non-naturally occurring nucleic acid further comprises a nucleotide sequence encoding a mitochondrial targeting sequence.

10 12. The non-naturally occurring nucleic acid of claim 1, wherein the non-naturally occurring nucleic acid further comprises a promoter operably linked to the nucleotide sequence.

15 13. The non-naturally occurring nucleic acid of claim 1, wherein the non-naturally occurring nucleic acid further comprises an enhancer element.

14. The non-naturally occurring nucleic acid of claim 1, wherein the non-naturally occurring nucleic acid further comprises a polyA tail.

20 15. A cell into which has been introduced a non-naturally occurring nucleic acid comprising a nucleotide sequence that (a) encodes a functional ND4 mitochondrial protein and (b) that differs from a naturally occurring nucleic acid that encodes a ND4 mitochondrial protein by at least one codon substitution.

25 16. The cell of claim 15, wherein the cell is a human cell.

17. The cell of claim 16, wherein the cell is a human nerve cell.

30 18. The cell of claim 17, wherein the human nerve cell is located in the optic nerve of a human subject.

19. A method for reducing dysfunction in a cell caused by a mtDNA mutation associated with Leber Hereditary Optic Neuropathy, the method comprising the steps of:

(a) providing a cell having a gene comprising the mtDNA mutation;

and

5 (b) introducing into the cell a sufficient amount of a non-naturally occurring nucleic acid comprising (i) a nucleotide sequence that encodes a functional ND4 mitochondrial protein and that differs from a naturally occurring nucleic acid that encodes a ND4 mitochondrial protein by at least one codon substitution and (ii) a nucleotide sequence that encodes a mitochondrial targeting sequence.

10

20. The method of claim 19, wherein the non-naturally occurring nucleic acid further comprises a promoter operably linked to the nucleotide sequence that encodes a functional ND4 mitochondrial protein.

15

21. The method of claim 19, wherein the non-naturally occurring nucleic acid further comprises an enhancer element.

22. The method of claim 19, wherein the non-naturally occurring nucleic acid further comprises a polyA tail.

20

23. The method of claim 19, wherein the cell is a human cell.

24. The method of claim 23, wherein the cell is a human nerve cell.

25

25. The method of claim 24, wherein the human nerve cell is located in the optic nerve of a human subject.